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Atty. Dkt. No.: 8600-0010
Client Dkt. No.: 00-0312 01 US

PATENT

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12/7/05 Michelle Hobson
Date Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Examiner: J. Baxter
LEE	Group Art Unit: 3731
Serial No.: 09/749,980	Confirmation No.: 6822
Filing Date: December 27, 2000	Customer No.: 20855
Title: BIOACTIVE MATERIALS FOR ANEURYSM REPAIR	

TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

Transmitted herewith for filing, please find the following documents:

X Appeal Brief (16 pages) with Claims Appendix (4 pages), Evidence Appendix (5 pages) and Related Proceedings Appendix (1 page)

X Return receipt postcard

The fee is calculated as follows:

	NO. OF CLAIMS	CLAIMS PREVIOUSLY PAID FOR	EXTRA CLAIMS	RATE	FEE
Total Claims	21	- 36	0	x $50.00	$0
Independent Claims	3	- 3	0	x $200.00	$0
Multiple dependent claims not previously presented, add $360.00					$0
Total Amendment Fee					$0
Petition for Extension of Time Fee					$0
Appeal Brief Fee					$500.00
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TOTAL FEE DUE					$500.00

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The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 18-1648.

Respectfully submitted,

Date: December 7, 2005

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APPEAL BRIEF

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APPEAL BRIEF

Mail Stop Appeal Brief
Commissioner for Patents
Alexandria, VA 22313

Sir:

INTRODUCTION

Appellants submit one copy of their brief on appeal in accordance with Section 41.37 (69 Fed. Reg. 49962, Aug 2004). All claims were finally rejected under 35 U.S.C. § 103 in a Final Office Action dated August 19, 2005. A Notice of Appeal was filed November 10, 2005, making an Appeal Brief due on or before January 10, 2006. Accordingly, this Brief is timely filed. Appellants respectfully request that the decision of the Examiner be reversed.

I. REAL PARTY IN INTEREST

Scimed Life Systems, the assignee of record of the above-referenced patent application, is the real party in interest in this matter.

II. RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any related appeals or interferences.

III. STATUS OF THE CLAIMS

Claims 1, 5-11, 14-16, 19, 22-24, 31, 32 and 34-37 are pending in the above-referenced case (hereinafter "the application"). The application was originally filed on December 27, 2000 with claims 1-30. In response a Restriction Requirement (mailed on April 4, 2002), claims 1-24 were elected, with traverse. Claims 1 and 21 were amended and claims 31-36 were added in an Amendment submitted on June 24, 2002. Claims 2, 12, 13, 20 and 33 were canceled, without prejudice or disclaimer and claims 1, 3, 11, 17, 21, 31 and 34 were amended in an Amendment submitted on November 22, 2002. In an Amendment filed March 31, 2003 (in response to a Final Office Action mailed on February 10, 2003) and re-filed with an RCE (mailed May 9, 2003), claim 18 was canceled without prejudice or disclaimer and claims 31, 32, 34 and 35 were amended. Claims 1, 4 and 21 were amended and claim 37 was added in a paper filed July 18, 2003. Claim 37 was amended and claim 17 was canceled in an Amendment after Final filed November 19, 2003. A second RCE was filed on December 12, 2003 to enter the amendments. An election of species requirement was mailed on March 8, 2004 and Appellants made a provisional election, with traverse, in a paper filed March 31, 2004. Claims 1 and 31 were amended in an Amendment filed May 18, 2004 and again in an Amendment after Final filed November 10, 2004. A third RCE was filed on January 10, 2005 to enter the amendments made after Final. Claim 1 was amended in a paper filed May 24, 2005. No amendments to the claims

were made in response to the Final Office Action mailed August 19, 2005. Accordingly, claims 1, 5-11, 14-16, 19, 22-24, 31, 32 and 34-37 are pending as shown in the Claims Appendix. Claims 1, 7-11, 14-16, 19, 23 and 24 are under active examination and remain rejected under 35 U.S.C. § 103(a).

IV. STATUS OF THE AMENDMENTS

In response to the Examiner's Final Office Action mailed August 19, 2005, Appellants filed a Response with arguments and no amendments. An Advisory Action was mailed on October 13, 2005. Thus, all claims remained rejected for the reasons set forth in the Final Office Action and Advisory Action and have not been amended since the Final Office Action.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The claimed subject matter relates to vaso-occlusive compositions.

The invention includes compositions consisting of: (1) a vaso-occlusive member selected from the group consisting of one or more vaso-occlusive coil, one or more filters, and combinations thereof (page 5, lines 8-10); and (2) a bioactive material selected from the group consisting of fibrin (page 4, line 16); polyethylene glycol derivatives (page 4, lines 16-17) ; thrombin-coated gelatin granules (page 4, line 17); balloons coated with iron microspheres (page 4, line 17); trace metals (page 4, line 18); thrombus-stabilizing molecules (page 4, line 18); and combinations thereof (page 4, line 18). The bioactive materials are not contained in separate layers (page 8, lines 12-22). The trace metal may be, for example, copper (page 5, lines 18-19). The thrombus-stabilizing molecule may be, for example, Factor XIII or functional fragments thereof; plasminogen activator inhibitor-1 (PAI-1) or functional fragments thereof; and/or α_2-antiplasmin or functional fragments thereof (page 5, lines 18-19). The bioactive material(s) may be adsorbed to the vaso-occlusive member (page 5, lines 3-4). In addition, the vaso-occlusive

member may be plasma treated, subject to ion implantation, and/or microtextured (page 5, lines 6-10).

The claims also relate to a method of occluding a vessel comprising administering to a subject in need thereof a vaso-occlusive composition described above (page 5, lines 11-14), for example, methods involving administering a composition consisting of a vaso-occlusive coil and/or filter and a copper or methods involving administering a composition consisting of a vaso-occlusive coil and/or filter and a thrombus-stabilizing molecule selected from the group consisting of Factor XIII, α_2-antiplasmin, plasminogen activator inhibitor-1 (PAI-1), combinations thereof and functional fragments thereof (page 5, lines 15-20). The vessel occluded may be an aneurysm (page 5, lines 13-14).

The invention also relates to a vaso-occlusive compositions comprising a vaso-occlusive coil, a liquid embolic material and an additional bioactive material selected from the group consisting of DNA; RNA; functional fragments of DNA, RNA, or cytokines; and combinations thereof, wherein at least one of the bioactive materials is attached to the vaso-occlusive coil (page 4, line 25 to page 5, line 5). The liquid embolic material may be a particulate material selected from the group consisting of microspheres, granules and beads (page 6, lines 21 to 24). In addition, the vaso-occlusive coil and/or particulate material(s) may be absorbable (page 10, line 24-25). The claims also relate to methods of occluding a vessel comprising administering to a subject in need thereof a vaso-occlusive composition as described above (page 5, lines 11-14).

The invention also relates to a vaso-occlusive composition comprising a vaso-occlusive member selected from the group consisting of one or more vaso-occlusive coils, one or more filters, one or more retention devices and combinations thereof (page 5, lines 9-10); and thrombin-coated gelatin granules or balloons coated with iron microspheres (page 4, line 17).

VI. GROUNDS OF REJECTION

1. Claims 1, 7, 8 and 11 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No.5,660,873 (hereinafter "Nikolaychik").

2. Claim 14 was rejected as obvious over Nikolaychik in view of U.S. Patent No. 6,231,590 (hereinafter "Slaikeu").

3. Claim 15 was rejected as obvious over Nikolaychik in view of U.S. Patent No. 5,891,192 (hereinafter "Murayama").

4. Claim 16 was rejected as obvious over Nikolaychik in view of U.S. Patent No. 6,256,979 (hereinafter "Nikolchev").

5. Claims 1, 7, 8, 9, 10, 23 and 24 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,690,666 (hereinafter "Berenstein") in view of U.S. Patent No. 4,414,976 (hereinafter "Schwarz").

VII. ARGUMENTS

1. Summary of the *Claimed* Subject Matter

As summarized above, the subject matter of the examined claims encompasses vaso-occlusive compositions consisting of a vaso-occlusive coil and/or filter in combination with one of the recited materials (claims, 1, 7-11, 14-16) and to methods of using these vaso-occlusive compositions to occlude a vessel inside the body (claims 19, 23 and 24).

Thus, Appellants wish to clarify the Examiner's apparent misunderstanding that the subject matter of the examined claims somehow relates to vaso-occlusive compositions that may

include a stent. It appears that, despite the clear use of **closed** transitional language (*i.e.*, "consisting of"), the Examiner believes that the examined claims, which recite specific vaso-occlusive members (coils and/or filters), somehow include stents. In support of this assertion, the Examiner cited page 3 of the arguments section of the Response After Final along with page 4, lines 19-20 of the specification. (Advisory Action, continuation page of Box 11).

In fact, the examined claims are clear on their face that the vaso-occlusive device component is not a stent. Instead, it is clearly and unambiguously recited in the claims that the vaso-occlusive member is either a coil and/or filter. *See,* claim 1 of the Claims Appendix.

Moreover, stents are not considered vaso-occlusive members by Appellants or by the skilled artisan. Appellants argument on page 3 of their Response After Final established that stents and vaso-occlusive coils and filters (as claimed) serve opposite purposes as implantable devices. The citation from Nikolaychik regarding stents inducing blockage was cited to show that Nikolaychik (and those working in the field) considered any vaso-occlusion to be highly undesirable effects of stents and, accordingly, was working to eliminate such effects. For its part, page 4, lines 19-20 of Appellants' specification, the only reference to stents in the entire application, is provided as one example of an implantable device.

In sum, stents are not encompassed by the examined claims because the claims are at issue are directed to a vaso-occlusive composition consisting of a vaso-occlusive coil or filter, not a stent. *See*, Claims Appendix.

2. A *Prima facie* Case of Obviousness Has Not been Established

Therefore, when the claims are properly construed, it is clear that the rejections based on Nikolaychik's disclosure of fibrin-coated stents cannot render obvious any of the pending claims to vaso-occlusive compositions and, indeed, teaches away from vaso-occlusive compositions as claimed. Similarly, the rejection based on Berenstein in view Schwarz is also untenable in that there is no combination of these references that teaches of suggests the subject matter of the examined claims.

The Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Ryckaert,* 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); and *In re Oetiker,* 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). In addition, the law is well settled that references must teach all the limitations of the claimed invention and, moreover, suggest the desirability of arriving at the claimed subject matter. (*See, e.g., Amgen, Inc. v. Chugai Pharm. Co.,* 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) stating that "hindsight is not a justifiable basis on which to find that the ultimate achievement of a long sought and difficult scientific goal was obvious;" *In re Laskowski,* 10 USPQ2d 1397, 1399 (Fed. Cir. 1989) stating that "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification"; and *In re Fulton*, 391 F.3d 1195 (Fed. Cir. 2004) stating that "[t]he question is whether there is something in the prior art as a whole to suggest the desirability").

In the pending case, the Examiner has not met this burden and the rejections cannot be maintained.

(a) The Rejections Based On Nikolaychik Are Based On Improper Picking and Choosing of Individual Elements

When the claims are properly construed, it is clear that Nikolaychik does not, alone or in combination with any of the secondary references, teach or suggest vaso-occlusive compositions as claimed, in which a vaso-occlusive member and one of the recited bioactive materials work together to occlude a vessel.

It is axiomatic that statements in the references must be considered in the context of the teaching of the entire reference, and that rejection of claims **cannot** be predicated on mere identification in a reference of individual components of claimed limitations. In this regard, the Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. *See, e.g., In re Kotzab* 217 F.3d 1365, 55 USPQ2d 1313, 1317 (CAFC 2000, emphasis added):

> While the test for establishing an implicit teaching, motivation or suggestion is what the combination of these two statements [in the reference] would have suggested to those of ordinary skill in the art, the two statements cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection **cannot** be predicated on the mere identification [in the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

Furthermore, it is well settled that reference must be considered for everything it teaches as a whole a reference must be used for what it teaches as a whole. *See, e.g., In re Wesslau*, 47 USPQ 391 (CCPA 1965) holding that "it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." Thus, a reference must be taken for all that it teaches or suggests. *See, e.g., Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*, 230 USPQ 416, 420 (Fed. Cir. 1986). Further, functional limitations in the claims must be evaluated and considered, just as any other claim limitation, for what is fairly conveyed to the skilled artisan in context. (See, e.g., MPEP 2173.05(g) Functional Limitations, Eighth Edition).

Thus, the requirement is not whether each claimed element can be identified individually in a reference but, rather, whether the Examiner can show "reasons that the skilled artisan, confronted with the same problem as the inventor, and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed." *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998).

In the pending case, the Office has not met this burden. The fact remains that Nikolaychik clearly and unambiguously teaches devices which have the opposite function to that claimed – Nikolaychik's stents are designed to keep vessels open while the claimed vaso-occlusive coils and filters are designed to block (occlude) a vessel. (See, also, Evidence

Appendix A: Dictionary definitions attached to Response filed November 21, 2002 of "stent" indicating that the function of a stent is to prevent occlusion).

Moreover, the fibrin coating Nikolaychik teaches for stents serves an entirely differently function than using fibrin in combination with a vaso-occlusive coil or filter as claimed. Indeed, Nikolaychik clearly teaches that the fibrin coating **reduces** occlusion of the vessel by the stent (see, *e.g.*, col. 1, lines 27-55 and col. 3, lines 39-50, emphasis added):

> The use of stents to **reopen** or **replace** the blocked portion of the blood vessel can create complications. Stents can themselves induce partial or complete blocking of the blood vessel by triggering blood clotting in the vicinity of the stent. After implantation, the natural process of fibrin deposition on the stent occurs to initiate the healing process. The deposition of the fibrin in the presence of thrombin triggers platelet activation and the formation of a thrombus or embolus. Bound thrombin can also induce the formation of more fibrin on the stent, thereby narrowing the luminal area of the stent. The reduced luminal area can cause an embolism in the patient.
>
> Several approaches have been employed to overcome the complications associated with vascular stents. In one approach, an anticoagulant is administered to the patient to reduce the likelihood of clotting. ... In yet another approach, a fibrin coating is deposited on the stent before implantation to facilitate the healing process. Compared to stents implanted without a fibrin coating, the incorporation of a fibrin coating on an implanted stent reduces significantly the likelihood of blood vessel **blockage** after implantation. ...
>
> The present invention has several advantages over existing substrates to be implanted in a living body. The incorporation of a fibrin coating on substrates of the present invention creates a low risk of blood clot formation after implantation of the substrate. The fibrin coatings of the present invention further provide a suitable environment for seeding the substrate with endothelial cells to reduce the thrombogenicity of the substrate. ... Finally, the fibrin coatings of the present invention can contain a substantial amount of natured fibrin and a limited amount of denatured fibrin. The presence of natured fibrin in the coating reduces the thrombogenicity of the coating.

Thus, the structure and function of Nikolaychik's fibrin coated stents are the complete opposites of the structure and function of the claimed fibrin-vaso-occlusive coil/filter.

Nikolaychik's compositions function to reduce vaso-occlusive effects while the claimed compositions function to promote vaso-occlusion.

The Office cannot ignore the fact that there is no motivation to look to Nikolaychik and actually a **teaching away** by this reference inasmuch as Nikolaychik's disclosure of coating stents with fibrin to reduce vaso-occlusion would lead one of skill in the art **away** from using fibrin in combination with a vaso-occlusive coil or filter in order to occlude a vessel, as claimed. To somehow assert that the skilled artisan reading a patent entitled "Coating Intraluminal Stents" which clearly teaches that fibrin coatings on stents reduce vaso-occlusivity of these stents would in some way be motivated use fibrin in combination vaso-occlusive coils or filters is unsustainable.

Thus, when taken as a whole, Nikolaychik is directed to completely different devices with completely different functions than the compositions claimed by Applicants. Accordingly, the skilled artisan would not (and indeed could not) have been motivated from Nikolaychik, alone or in combination with Slaikeu, Murayama, or Nikolchev, to arrive at the invention as claimed, because the proposed modification would destroy the intended function of Nikolaychik's stents. Since these rejections can only be predicated on the mere identification of individual components without the motivation to combine them into the vaso-occlusive compositions. This is entirely improper and the rejections should be withdrawn.

(b) There Is No Motivation To Combine Berenstein and Schwarz As Set Forth in the Rejection

As noted above, examined claims 1, 7, 8, 9, 10, 23 and 24 have also been rejected based on the allegation that the combined teachings of Berenstein and Schwarz render these claims obvious. (Final Office Action, paragraph 3). Berenstein was cited for allegedly disclosing a vaso-occlusive coil that is used with a tissue adhesive while Schwarz is cited for teaching that a surgical tissue adhesive can be made with Factor XIII, plasminogen activator or plasmin inhibitor in order to stimulate wound healing. *Id.* It was alleged that it would have been obvious

to provide the device of Berenstein with the tissue adhesive of Schwarz in order to promote wound healing. *Id.*

In response to Appellants' previous arguments that there is no motivation to combine these references as set forth in the rejection, the Examiner stated that the motivation to combine these references as set forth derives from the fact that both use tissue adhesives in the vascular system (Final Office Action, paragraph 8):

> Applicant argues that Berenstein cannot be combined with Schwarz since there is no suggestion to combine. The examiner maintains that one would be motivated to combine Schwarz with Berenstein, since Berenstein uses tissue adhesives (see abstract) and Schwarz teaches a tissue adhesive that is used in the vascular system to stimulate healing (col. 2, line 64 to column 3, line 7).

The alleged motivation to combine the references (namely, that both teach tissue adhesives, albeit completely different tissue adhesives) blatantly ignores the critical axioms of an obviousness inquiry, namely whether the references or art suggest the ***desirability*** of the claimed invention, not merely whether the individual elements are all set forth. *See, e.g., Amgen, Inc. v. Chugai Pharm. Co.,* 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) stating that "hindsight is not a justifiable basis on which to find that the ultimate achievement of a long sought and difficult scientific goal was obvious;" *In re Laskowski,* 10 USPQ2d 1397, 1399 (Fed. Cir. 1989) stating that "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification"; and *In re Fulton*, 391 F.3d 1195 (Fed. Cir. 2004) stating that "[t]he question is whether there is something in the prior art as a whole to suggest the desirability."

The fact remains that there is nothing in either Berenstein or Schwarz that would suggest the **desirability** of replacing Berenstein's cyanoacrylate polymer resin for use in unexposed vessels (*e.g.,* aneurysm) with Schwarz's Factor VII containing compositions for stopping bleeding and sealing wounds of exposed tissue and organs. As admitted by the Office, Berenstein does not teach or suggest thrombus-stabilizing molecules as claimed. Rather,

Berenstein discloses that a particular type of tissue adhesive, namely a cyanoacrylate resin, may be injected into a vessel after the ultrasoft coil substrate has been introduced. The only example of a suitable "tissue adhesive" for the disclosed occlusive function is a cyanoacrylate polymer resin (*see*, col. 5, line 66 to col. 6, line 6 of Berenstein, emphasis added):

> Additionally, this process may include the step of introducing polymer resins, such as cyanoacrylate resins (particularly n-butylcyanoacrylate) to the intended site after the inventive coils or braids are in place. Said another way, the inventive coils or braids form a substrate for these **tissue adhesives**, or particulate embolization materials such as microparticles of polyvinyl alcohol foam, or various chemotherapeutic agents.

For its part, Schwarz is completely silent as to coils or vessel occlusion, disclosing instead a tissue adhesive comprising fibrinogen and Factor VIII to "seamlessly connecting tissue or organ parts, for sealing wounds, stopping bleeding and stimulating wound healing in mammals." *See,* claim 1 of Schwarz.

There is no suggestion in either reference that cyanoacrylate resins and Factor VIII-fibrinogen compositions are interchangeable. Moreover, the basis of this rejection, namely that the motivation to combine the references derives from the fact that both Berenstein's cyanoacrylate resins and Schwarz's composition are used to stimulate healing in the vascular system, is contradicted by the references themselves. Indeed, contrary to the Examiner's assertion, the cited references **teach away** from any interchangeability of infused cyanoacrylate polymers (Berenstein) and Factor VIII-containing compositions (Schwarz). Whereas Schwarz's tissue adhesives are applied directly to an exposed site (*i.e.,* surface wound or organ exposed during surgery), Berenstein teaches only cyanoacrylate resins because they were known to be deliverable to a remote vessel. The skilled artisan reading Berenstein would not be motivated to replace the cyanoacrylate resins with any topical tissue adhesives (such as Schwarz). Instead, the skilled artisan would have clearly recognized that Schwarz did not suggest infusing Factor VIII-containing compositions to occlude a vessel that was not directly exposed to the surgeon. As

such, there is no motivation to substitute Schwarz's Factor VIII-fibrinogen composition for Berenstein's cyanoacrylate resins because the two compositions have clearly different indications and a skilled artisan would not have recognized a topical tissue adhesive (Schwarz) as a substitute for an infuseable cyanoacrylate resin (Berenstein).

Simply identifying the various elements of a claim in separate documents is **not** enough to support a *prima facie* case of obviousness. Absent the suggestion that it would be desirable to combine surface tissue adhesives (such as Schwarz's) with vaso-occlusive coils for use in non-surface indications (such as Berenstein's), the rejection can only be based on improper hindsight reconstruction. Without the benefit of Appellants' disclosure, there is no motivation or suggestion regarding the desirability of substituting Schwarz's surface tissue adhesives for Berenstein's cyanoacrylate resins. Accordingly, a *prima facie* case of obviousness has not been (and indeed cannot be) presented by the Office. Withdrawal of the rejection is in order.

CONCLUSION

For the reasons stated above, Appellants respectfully submit that the pending claims are non-obvious over the cited references. Accordingly, Appellants request that the rejections of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

Date: December 7, 2005

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CLAIMS APPENDIX

CLAIMS INVOLVED IN THE APPEAL

1. (previously presented): A vaso-occlusive composition consisting of

a vaso-occlusive member selected from the group consisting of one or more vaso-occlusive coils, one or more filters, and combinations thereof; and

a bioactive material selected from the group consisting of fibrin; polyethylene glycol derivatives; thrombin-coated gelatin granules; balloons coated with iron microspheres; trace metals; thrombus-stabilizing molecules; and combinations thereof, wherein combinations of bioactive materials are not contained in separate layers and wherein the vaso-occlusive member is selected from the group consisting of one or more vaso-occlusive coils, one or more filters, and combinations thereof.

2 to 4. (canceled).

5. (withdrawn): The composition of claim 1, wherein the material comprises a trace metal.

6. (withdrawn): The composition of claim 5, wherein the trace metal comprises copper.

7. (original): The composition of claim 1, wherein the material comprises a thrombus-stabilizing molecule.

8. (original): The composition of claim 7, wherein the thrombus-stabilizing molecule is Factor XIII or functional fragments thereof.

9. (original): The composition of claim 7, wherein the thrombus-stabilizing molecule is plasminogen activator inhibitor-1 (PAI-1) or functional fragments thereof.

10. (original): The composition of claim 7, wherein the thrombus-stabilizing molecule is

α_2-antiplasmin or functional fragments thereof.

11. (previously presented): The composition of claim 1, wherein the bioactive material is adsorbed to the vaso-occlusive member.

12 to 13. (canceled)

14. (original): The composition of claim 1, wherein the vaso-occlusive member is plasma treated.

15. (original): The composition of claim 1, wherein the vaso-occlusive member is subjected to ion implantation.

16. (original): The composition of claim 1, wherein the vaso-occlusive member is microtextured.

17 to 18. (canceled).

19. (original): A method of occluding a vessel comprising administering to a subject in need thereof a vaso-occlusive composition according to claim 1.

20 to 21. (canceled).

22. (withdrawn): The method of claim 19, wherein the trace metal is copper.

23. (original): The method of claim 19, wherein the thrombus-stabilizing molecule is selected from the group consisting of Factor XIII, α_2-antiplasmin, plasminogen activator inhibitor-1 (PAI-1), combinations thereof and functional fragments thereof.

24. (original): The method of claim 19, wherein the vessel is an aneurysm.

25 to 30. (canceled)

31. (withdrawn): A vaso-occlusive composition comprising a vaso-occlusive coil, a liquid embolic material and an additional bioactive material selected from the group consisting of DNA; RNA; functional fragments of DNA, RNA, or cytokines; and combinations thereof, wherein at least one of the bioactive materials is attached to the vaso-occlusive coil.

32. (withdrawn): The vaso-occlusive composition of claim 31, wherein the liquid embolic material is a particulate material selected from the group consisting of microspheres, granules and beads.

33. (canceled).

34. (withdrawn): The vaso-occlusive composition of claim 31, wherein the vaso-occlusive coil is absorbable.

35. (withdrawn): The vaso-occlusive composition of claim 32, wherein the particulate material is absorbable.

36. (withdrawn): A method of occluding a vessel comprising administering to a subject in need thereof a vaso-occlusive composition according to claim 31.

37. (withdrawn): A vaso-occlusive composition comprising

a vaso-occlusive member selected from the group consisting of one or more vaso-occlusive coils, one or more filters, one or more retention devices and combinations thereof; and

thrombin-coated gelatin granules or balloons coated with iron microspheres.

EVIDENCE APPENDIX

Evidence Appendix A: Dictionary definitions of the term "stent." This evidence was attached to Response to non-Final Office Action filed November 21, 2002, which Response was indicated by the Examiner to have been considered in a Final Office Action dated February 10, 2003.

Edition
28

Dorland's *Illustrated* Medical Dictionary

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Philadelphia London Toronto Montreal Sydney Tokyo

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A Division of Harcourt Brace & Company

The Curtis Center
Independence Square West
Philadelphia, PA 19106

Dorland's illustrated medical dictionary.
Philadelphia: W.B. Saunders Co.,
v.: ill.; 27 cm.
Irregular.
Began publication with 23rd ed.
Description based on: 26th ed.
Continues: American illustrated medical dictionary.

1. Medicine—Dictionaries. I. Dorland, W.A. Newman (William Alexander Newman), 1864–1956.
[DNLM: 1. Dictionaries, Medical. 2. Reference Books, Medical]

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AACR 2 MARC-S

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Italian *(27th Edition, revised)*—Edizioni Scientifiche Internazionali (ESI), Milan, Italy

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for transmitting occlusal stresses parallel to its long axis and holding the clasp in its predetermined position; a component of removable partial dentures. Called also *occlusal stop.*

precision r., a prefabricated, rigid, metallic extension of a fixed or removable partial denture, consisting of two closely fitted interlocking parts, the insert of which fits into a box-type rest or keyway (female) portion of the attachment in the cast restoration of a tooth.

recessed r., a rigid extension of a partial denture which contacts a definite seat prepared in the surface of a tooth.

semiprecision r., a denture rest, sometimes supplemented by a spring-loaded plunger or clip, which fits into a seat in an abutment tooth that has been specially deepened to provide added retention. See also under *attachment.*

suprarenal r., adrenal r.

surface r., a rigid extension of a partial denture which contacts the unaltered extracoronal surface of a tooth.

Walthard's cell r's, see under *islet.*

rest·bite (rest'bīt) the relation of the teeth when the jaw is at rest.

re·ste·no·sis (re"stə-no'sis) recurrent stenosis, especially of a valve of the heart, after surgical correction of the primary condition.

false r., stenosis recurring after failure to divide either commissure of the cardiac valve beyond the area of incision of the papillary muscles.

true r., restenosis occurring after complete opening of one or both of the commissures of the cardiac valve involved.

res·ti·form (res'tĭ-form) [L. *restis* rope + *forma* form] shaped like a rope.

res·ti·tu·tion (res"tĭ-too'shən) [L. *restitutio*] 1. an active process of restoration. 2. the spontaneous realignment of the fetal head with the fetal body, after delivery of the head.

res·to·ra·tion (res"tə-ra'shən) [L. *restaurare* to review, rebuild] 1. the act of renewing, rebuilding, or reconstructing. 2. the return to a previous state or condition, as of health. 3. the process of replacing by artificial means a missing, damaged, or diseased tooth or teeth or any part thereof. See also *prosthetic r.* and *restorative dentistry,* under *dentistry.* 4. the act of re-forming the contours of parts of teeth destroyed by lesions or injury, thereby restoring their functional properties.

buccal r., the replacement, usually with silver alloy, gold, or plastic, of the buccal portion of a posterior tooth lost through caries or injury.

cusp r., restoration of the summit of a cusp or the incisal edge of a tooth, done for functional or cosmetic reasons.

facial r., the replacement, usually with silver alloy, gold, or acrylic resin, of the facial portion of a posterior tooth lost through caries or injury.

prosthetic r., 1. the replacement of a lost or absent body part with an artificial structure, such as the use of an inlay, crown, bridge, or partial or complete denture, or other appliance to replace lost tooth structure, teeth, or oral tissue or structure. 2. any appliance, such as an inlay, crown, bridge, or partial or complete denture, used to replace lost tooth structure, teeth, or oral tissue or structure.

Res·tor·il (res'tə-ril") trademark for a preparation of temazepam.

re·straint (re-strānt') the forcible confinement of a violently psychotic or irrational person.

re·stric·tion (re-strik'shən) 1. anything that limits; also, a limitation. 2. see *restriction endonuclease,* under *endonuclease.*

intrauterine growth r., see under *retardation.*

MHC r., the phenomenon of certain cell-cell interactions in the immune response occurring only between MHC haploidentical cells. Helper T cells are activated by antigen only when the antigen is "seen" in conjunction with self class II MHC antigens (Ia antigens in mice, HLA-DR antigens in humans) as is the case when antigen is presented by macrophages. Cytotoxic T cells are activated by and kill only cells displaying foreign antigens (e.g., viral antigens or tumor antigens) plus self class I MHC antigens (K or D antigens in mice, HLA-A, -B, or -C antigens in humans).

re·sub·limed (re"səb-līmd') subjected to repeated processes of sublimation.

re·sul·tant (re-zul'tənt) any of the products of a chemical reaction.

re·su·pi·na·tion (re"soo-pī-na'shən) [L. *resupinare* to turn on the back] 1. the act of turning upon the back or dorsum. 2. the position of one lying upon the back.

re·sus·ci·ta·tion (re-sus"ĭ-ta'shən) [L. *resuscitare* to revive] the restoration to life or consciousness of one apparently dead; it includes such measures as artificial respiration and cardiac massage.

cardiopulmonary r. (CPR), the artificial substitution of heart and lung action as indicated for cardiac arrest or apparent sudden death resulting from electric shock, drowning, re and other causes. The two major components of ventilation and closed chest cardiac massage; see

re·sus·ci·ta·tor (re-sus'ĭ-ta"tor) an apparatus for tion in cases of asphyxia.

cardiopulmonary r., an apparatus that simultane patient's breathing and applies external cardiac n

re·su·ture (re-soo'chər) secondary suture.

re·tain·er (re-ta'nər) 1. a device for retaining or k in position. 2. the part of a denture that unites th with the suspended portion of the bridge, such a crown, or complete crown. 3. an orthodontic devi in position the teeth and jaws. 4. any form of clas other device used for the fixation or stabilizatio appliance. 5. the portion of a fixed prosthesis atta the abutment teeth.

continuous bar r., continuous clasp.

direct r., a clasp or attachment applied to an ab which a removable partial denture is maintained

Hawley r., an orthodontic appliance consisting o latal wire and an acrylic biteplate resting against t stabilize teeth after their movement or as a basi ment by providing anchorage for other attachm *Hawley appliance.*

indirect r., a part of a removable partial denture direct retainers in preventing displacement of dist ture bases by functioning through lever action on of the fulcrum line.

matrix r., a mechanical device designed to enga matrix band or strip and to tighten the matrix arc

space r., an orthodontic appliance that retains the premature loss of a tooth or the space to be fille tooth. See also under *maintainer* and *regainer.*

re·tar·date (re-tahr'dāt) a mentally retarded per

re·tar·da·tion (re"tahr-da'shən) [L. *retardare* to pede] delay; hindrance; delayed development.

intrauterine growth r. (IUGR), birth weight below tile for gestational age for infants born in a given p fied as *symmetric* (both weight and length below *metric* (weight below normal, length norma *intrauterine growth restriction.*

mental r. [DSM-III-R], a mental disorder charact cantly subaverage general intellectual functionin impairments in adaptive behavior and manifested opmental period; classified as *mild* (IQ 50–70)—c and communication skills during the preschool p mal sensorimotor impairment, can by their late demic skills up to the sixth grade level, and usua and vocational skills adequate for minimal self-s (IQ 35–50)—can talk or learn to communicate but awareness and only fair motor development; ar gress to the second grade level in academic ski from vocational training, and can take care of t supervision; *severe* (IQ 20–35)—have poor mo and minimal speech in the preschool period; ma their late teens and can be trained in elementary h as adults may learn to perform simple work und sion; *profound* (IQ below 20)—have limited sensc ment, may achieve very limited self-care, and requ tured environment and constant supervision. *B* retardation (IQ 70–85), now called borderline int ing, is used to refer to very mild forms with only s in adaptive behavior. Called also *mental deficier ity.*

psychomotor r., generalized slowing of mental a ity; seen in depression.

retch·ing (rech'ing) a strong involuntary effort to

re·te (re'te) pl. *re'tia* [L. "net"] a net or meshwork cal nomenclature as a general term to designate cially of arteries or veins.

acromial r., r. acromia'le [NA], a network formed the acromial branch of the thoracoacromial artery process.

r. arterio'sum [NA], an anastomotic network form before they become arterioles or capillaries.

articular r., r. vasculosum articulare.

articular cubital r., articular r. of elbow, r. articu

articular r. of knee, r. articulare genus.

r. articula're cu'biti [NA], articular rete of elbo work formed on the posterior aspect of the elbow ulnar recurrent, inferior and superior ulnar coll osseous recurrent arteries.

r. articula're ge'nus [NA], articular rete of knee: rial rete on the capsule of the knee joint, supplyin

steno·ceph·a·ly (sten″o-sef′ə-le) [*ste*… + Gr. *kephalē* head] excessive narrowness of the head.

steno·cho·ria (sten″o-kor′e-ə) [*steno-* + Gr. *chōros* space] stenosis, or narrowing.

steno·co·ri·a·sis (sten″o-kə-ri′ə-sis) [*steno-* + Gr. *korē* pupil] contraction of the pupil of the eye.

steno·cro·ta·phia (sten″o-kro-ta′fe-ə) [*steno-* + Gr. *krotaphos* temple + *-ia*] narrowness of the temporal region.

steno·crot·a·phy (sten″o-krot′ə-fe) stenocrotaphia.

steno·pe·ic (sten″o-pe′ik) [*steno-* + Gr. *opē* opening] having a narrow slit or opening, as stenopeic spectacles.

ste·no·sal (stə-no′səl) stenotic.

ste·nosed (stə-nōzd′) narrowed or constricted.

ste·no·sis (stə-no′sis) [Gr. *stenōsis*] narrowing or stricture of a duct or canal.

aortic s. (AS), narrowing of the orifice of the aortic valve or of the supravalvular or subvalvular regions; see also *supravalvular aortic s.* and *subvalvular aortic s.*

buttonhole mitral s., mitral stenosis in which adhesion and shortening of the mitral cusps produces a diaphragmatic slit resembling a buttonhole; called also *fishmouth mitral s.*

caroticovertebral s., atherosclerotic stenosis of the cervical portions of the vertebral arteries, resulting in cerebral ischemia.

cicatricial s., stenosis caused by the contraction of a cicatrix.

fishmouth mitral s., buttonhole mitral s.

granulation s., stenosis or narrowing caused by the deposit of granulations or by their contraction.

hypertrophic pyloric s., narrowing of the pyloric canal by muscular hypertrophy and mucosal edema, occurring chiefly in infants, and marked by nausea, vomiting, epigastric pain, anorexia, weight loss, dehydration, and hypochloremic alkalosis; in infants there are a palpable pyloric mass and visible peristalsis.

idiopathic hypertrophic subaortic s., a form of hypertrophic cardiomyopathy, in which the left ventricle is hypertrophied (commonly with disproportionate involvement of the interventricular septum) and the cavity is small; it is marked by obstruction to left ventricular outflow. Called also *muscular subaortic s.*

infantile hypertrophic gastric s., congenital hypertrophy and hyperplasia of the musculature of the pyloric sphincter, occurring within the first few weeks of life and leading to partial obstruction of the gastric outlet.

infundibular s., stenosis below the pulmonary valve, within the infundibulum (conus arteriosus) of the right ventricle of the heart.

mitral s., a narrowing of the left atrioventricular orifice (mitral orifice).

muscular subaortic s., idiopathic hypertrophic subaortic s.

postdiphtheritic s., stenosis of the larynx or trachea following diphtheria.

pulmonary s. (PS), narrowing of the opening between the pulmonary artery and the right ventricle, usually at the level of the valve leaflets.

pyloric s., obstruction of the pyloric orifice of the stomach; it may be congenital as in hypertrophic pyloric stenosis, or acquired due to peptic ulceration or prepyloric carcinoma.

spinal s., narrowing of the vertebral canal, nerve root canals, or intervertebral foramina of the lumbar spine caused by encroachment of bone upon the space; symptoms are caused by compression of the cauda equina and include pain, paresthesias, and neurogenic claudication. The condition may be either congenital or due to spinal degeneration. See also *spinal compression* under *compression.*

subaortic s., aortic stenosis due to an obstructive lesion in the left ventricle below the aortic valve, causing a pressure gradient across the obstruction within the ventricle.

subpulmonic infundibular s., infundibular s.

subvalvular aortic s., subaortic s.

supravalvular aortic s., a rare form of aortic stenosis occurring above the aortic valve, usually caused by a completely or incompletely differentiated fibrous ring of constricting tissue at the level of the sinuses of Valsalva. See also *Williams syndrome,* under *syndrome.*

tricuspid s. (TS), narrowing or stricture of the tricuspid orifice of the heart.

valvular s., stenosis affecting any of the valves of the heart; see *aortic s., mitral s., pulmonary s.,* and *tricuspid s.*

steno·ther·mal (sten″o-ther′məl) stenothermic.

steno·ther·mic (sten″o-ther′mik) [*steno-* + Gr. *therme* heat] capable of development only within a narrow range of temperature, as a bacterial culture.

steno·tho·rax (sten″o-thor′aks) [*steno-* + Gr. *thōrax* chest] abnormal narrowness of the chest.

ste·not·ic (stə-not′ik) [Gr. *stenotēs* narrowness] pertaining to or characterized by stenosis; abnormally narrowed.

sten·sen's canal, duct, etc. (sten′sənz) [Niels Stensen (Nicolaus Steno), Danish physician, anatomist in Italy, 1638–1686] see under *experiment* and *plexus,* and see *canalis incisivum, ductus parotideus,* and *foramen incisivum.*

stent (stent) [from Charles R. *Stent,* English dentist, died 1901] 1. a mold for keeping a skin graft in place, made of Stent's mass or some acrylic or dental compound. 2. a device or mold for keeping a skin graft in place. 3. a slender rod- or thread-like device used to provide support for tubular structures that are being anastomosed or to induce or maintain patency within these tubular structures.

step (step) one of a series of footrests on different levels, or a structure resembling it.

Rönne's nasal s., a steplike defect in the nasal side of the visual field; seen in glaucoma.

ste·pha·ni·al (stə-fa′ne-əl) pertaining to the stephanion.

ste·pha·ni·on (stə-fa′ne-ən) [Gr. *stephanos* crown + *-on* neuter ending] the point on the side of the cranium at which the coronal suture meets the superior temporal line.

Steph·a·no·fi·lar·ia (stef″ə-no-fi-lar′e-ə) a genus of filarial nematodes.

S. stile′si, a species causing dermatitis in cattle in the United States.

steph·a·no·fi·la·ri·a·sis (stef″ə-no-fil″ə-ri′ə-sis) a chronic skin disease of cattle in certain parts of the United States, due to infestation with the nematode *Stephanofilaria stilesi;* called also *verminous dermatitis.*

Steph·a·nu·rus (stef″ə-nu′rəs) a genus of nematode parasites of the family Syngamidae.

S. denta′tus, a species parasitic in the urinary tract and occasionally in other tissues of swine.

ste·ra·di·an (stə-ra′de-ən) [Gr. *ster-* solid + *radian*] the unit of measurement of solid angles, equivalent to the angle subtended at the center of a sphere by an area on its surface equal to the square of its radius. A full sphere subtends 4π steradians. Abbreviated sr.

Ster·ane (ster′ān) trademark for preparations of prednisolone.

Ster·a·pred (ster′ə-pred″) trademark for preparations of prednisone.

sterc(o)- [L. *stercus* dung] a combining form denoting relationship to feces.

ster·co·bi·lin (stər″ko-bi′lin) [*sterco-* + *bilin*] a bile pigment derivative, formed by air oxidation of stercobilinogen, which is in turn derived by reduction of bilirubin; it is a brown-orange-red pigmentation contributing to the color of feces and urine.

ster·co·bi·lin·o·gen (stər″ko-bi-lin′o-jən) a bilirubin metabolite and precursor of stercobilin, formed by reduction of urobilinogen.

ster·co·lith (stər′ko-lith) [*sterco-* + Gr. *lithos* stone] a fecal concretion.

ster·co·ra·ceous (stər″kə-ra′shəs) [L. *stercoraceus*] consisting of or containing feces; fecal.

ster·co·ral (stər′kə-rəl) stercoraceous.

ster·co·rar·ia (stər″kə-rar′e-ə) in some systems of classification, a group or section comprising those trypanosomes in which the developmental cycle is completed in the hindgut (posterior station) of the vector and transmission is by fecal contamination during biting of the host by the vector. The group includes the subgenera *Megatrypanum, Herpetosoma,* and *Schizotrypanum.* Cf. *salivaria.*

ster·co·rar·i·an (stər″kə-rar′e-ən) pertaining to or caused by trypanosomes of the stercoraria group or section.

ster·co·ro·lith (stər′kə-ro-lith) stercolith.

ster·co·ro·ma (stər″kə-ro′mə) a large accumulation of fecal matter forming a tumor-like mass in the rectum; called also *coproma, fecaloma,* and *scatoma.*

ster·co·rous (stər′kə-rəs) [L. *stercorosus*] of the nature of excrement.

ster·cu·lia (stər-ku′le-ə) a genus of trees and shrubs, including many species, mostly tropical; some have edible seeds and others are medicinal, while still others afford a gummy exudation with cathartic and adhesive properties (see *karaya gum,* under *gum*). The hairs of *S. apetala* of Panama may be very irritating.

ster·cus (stər′kəs) pl. *ster′cora* [L.] dung, or feces.

stere (stēr) [Gr. *stereos* solid] a cubic meter.

stereo- [Gr. *stereos* solid] a combining form meaning solid, having three dimensions, or firmly established.

RELATED PROCEEDINGS APPENDIX

As noted above on page 2 of this Brief on Appeal and pursuant to 37 C.F.R. § 41.37(c)(i) and (c)(x), Appellants are not aware of any related appeals or interferences which may be related to, directly affect, be directly affected by, or have any bearing on the Board's decision in the pending appeal. Accordingly, no documents are submitted with this Appendix.